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Perspectives in Cancer Research

Epidemiology, Basic Science, and the Prevention of Cancer: Implications for the Future

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Around 1618, Thomas Adams (1) wrote "He is a better physician that keeps diseases off us, than he that cures them being on us; prevention is so much better than healing because it saves the labour of being sick." This article examines the current and possible future world cancer burden, identifies the sites of cancer for which a better understanding of etiology is urgently needed, discusses the clamant need for greater collaboration between epidemiologists, clinicians, and basic scientists and sets these topics in the context of prevention, ending with a discussion on some of the problems currently facing epidemiology as a discipline.

The World Cancer Burden: Today and Tomorrow

Although national figures for cancer mortality have been available for many countries since the turn of the century, it was not until recently that any attempt was made to assess the world cancer burden (2). This estimate was recently updated (3) for 1980, when it was considered that there were likely to be around 6.35 million new cases of cancer each year, almost equally divided between the developed and developing world, where, however, two-thirds of the world's population lives. While there are wide differences in the pattern of cancer sites in the 24 demographic regions recognized by the United Nations for which Parkin *et al.* (3), present data, globally speaking, the first six ranking sites, which account for nearly 60% of the world cancer burden are given in Table 1.

Two of the leading sites in males, lung and mouth/pharynx, are largely due to the effects of tobacco, whether smoked or chewed (as in the Indian subcontinent) and abuse of alcohol. Cancer of the large bowel has been linked to diet as has that of the prostate. The incidence of female breast cancer, which seems to have stabilized in several western populations but is increasing rapidly in populations which have hitherto been at low risk, is also believed to have a dietary component. In contrast, cancer of the cervix uteri, although by far the commonest tumor in women of developing countries around 1980, seems to be falling in incidence nearly everywhere. Lung cancer, in sixth rank in females, is likely to become much commoner. If the two sexes be combined, stomach cancer occupies first place, being marginally more frequent than lung cancer. By the year 2000, given the virtually universal fall in the incidence of gastric cancer, even in countries such as Japan which have hitherto had very high rates, it is likely that lung cancer will be in first rank.

In many parts of the world, the average age of the population is rising. Because cancer is more common in older persons, the total number of persons with cancer will increase on demographic grounds alone. Muir (4) has estimated that given current demographic trends and trends in risk, eastern and southern Europe would have to face the prospect of providing the facilities and manpower for the diagnosis and treatment of about 60% more cancer in 2000 than in 1975. In the north and west of Europe, the increase will probably be around 15% as the major demographic changes have already taken place. Hakulinen *et al.* (5) present forecasts for Finland up to 2008 and discuss the models used and the assumptions made. Major demography-linked increases in the cancer burden in developing countries will not take place for some time because young persons will predominate for the next 30 years or so. No country, however prosperous, can face the social and economic costs involved in the diagnosis, treatment, and rehabilitation of ever increasing numbers of cancer patients, and the need for a reduction in their number is axiomatic.

The Pressing Problems

The causes of most lung cancers are known. For cancer of the stomach, case-control studies have repeatedly shown in several countries a protective effect for fresh fruit and vegetables. The analytical epidemiologist, believing that prevention is easier when cause is known, would thus wish to concentrate his efforts on the other common cancers, those of the large bowel, liver, breast, cervix uteri, and prostate. One might imagine that in a rational world there would be a major investment in the study of risk factors for these tumors.

However, a survey conducted by the IARC[1] showed that the sums spent on epidemiology compared to other forms of cancer research have hitherto been trivial, frequently less than 1% of national cancer research budgets (6). The National Cancer Institute devotes about 5% of its funds to epidemiology; IARC denotes some 45% (see also comment below).

These are other constraints. The induction period of cancer is a major obstacle to epidemiological progress. Although in a sense welcome, in that most forms of human malignancy seem to require continued exposure for a prolonged period, this phenomenon poses major logistic problems when mounting prospective cohort studies and assessing the effects of intervention as exposures and confounders change with time. Epidemiology is seen as painfully slow and rather imprecise and has, further, acquired a reputation of being expensive. In fact if one considers the time scale involved the contrary is true.

Epidemiological Research Tools Available

Case-Control Studies. The analytical epidemiologist has, in the ultimate analysis, but one technique at his disposal, namely, the prospective study. The widely used case-control study is, as Mantel and Haenszel (7) pointed out, in essence a prospective study with an end point at some arbitrary time which has yielded a series of cases, the controls being chosen from the remainder of the study population. The retrospective (frequently industrial) cohort study defines a group of persons sometime in the past and studies their subsequent cancer experience, usually comparing it with that of a general population of the same age

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[1] The abbreviations used are: IARC, International Agency for Research on Cancer; HPV, human papilloma virus.

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and sex composition followed over the same calendar period. The truly prospective study beginning now will frequently require many years before cases begin to appear (see below).

The epidemiological workhorse, the case-control study, may well, in its present form, be reaching the end of its utility. The golden age of epidemiology with large relative risks such as those observed following prolonged use of tobacco and the hepatitis B carrier state has probably passed. Increasingly, the relative risks uncovered are in the range of 1.5 to 2.5, an order of increased risk which could well be due to some undetected, unrecognized bias or confounding. Even comparatively large studies may not be large enough to yield sufficient cases in small sub-groups of interest. To this end, it is imperative that a substantial portion of case-control studies be multicenter, following a common core protocol as in the IARC-coordinated SEARCH Programme (8), and in the study of bladder cancer coordinated by the National Cancer Institute (9), and the WHO-sponsored multicenter study of breast cancer (10). This approach has many advantages. The planning phase, in which experienced investigators from several centers meet, ensures that all hypotheses are considered, even though they may not be examined. The multiplicity of centers ensures that sufficient cases are available for a pooled analysis. If there is a consistent increase in risk following some exposure in all or most of the study centers, then one has a greater confidence that the result is not likely to be due to bias or confounding, because it is unlikely that these factors would operate in the same way in all the centers. While the increasingly popular meta analysis of published studies can be rewarding, a multicenter study with a common agreed protocol is likely to be less liable to distortion and the problem of missing data. The use of a meta-analytic approach cannot supplant the performance of studies with adequate sample size. A collection of a series of small studies that reinforce each other may produce a false negative result due to the lack of power or a false positive result due to an illusion of comparability which is actually not present (11).

Mayes *et al.* (12) list 56 topics in which the results of a case-control study did not agree with the results from other studies of the same relationship. Cancer was the disease involved for 30 of the conflicting investigations. That there should be some disagreement is not surprising. Populations differ in their exposures and in the time of introduction of risk factors; bias and confounding operate in various ways and statistical chance may operate in more than one direction. Many studies simply do not have the inherent power to have a reasonable chance of detecting moderate elevations in risk. The fact that by the laws of probability "significant" findings may occur by chance alone or may fail to appear, again by chance alone, for some reason undermines the credibility of our discipline. Epidemiology is still somehow considered as being not truly scientific. By virtue of the fact that it is based on measurement, it is a science. The precision of the tools available for measurement, however, may be less than optimal, notably in the area of diet.

Table 1 *Most frequent cancers worldwide, 1980*

	Males			Females		
Rank	Site	No.[a]	%	Site	No.[a]	%
1	Lung	513.6	15.8	Breast	572.1	18.4
2	Stomach	408.8	12.6	Cervix	465.6	15.0
3	Colon/rectum	286.2	8.8	Colon/rectum	285.9	9.2
4	Mouth/pharynx	257.3	7.9	Stomach	260.6	8.4
5	Prostate	235.8	7.3	Corpus uteri	148.8	4.8
6	Esophagus	202.1	6.2	Lung	146.9	4.7
	All sites	3247		All sites	3103	

[a] In thousands.

Prospective Studies. The designer of the case-control study must bear in mind the *post hoc/propter hoc* question, in that the presence of viral antibody, hormonal and biochemical change may be the result of the disease rather than the cause. The case-control study is perhaps at its weakest when probing dietary hypotheses. As Jensen *et al.* (13) and others have so clearly shown, perceptions of diet in the past are very strongly influenced by recent consumption patterns. This would not be important if dietary patterns did not change over time, but this is not so. If we are not to drown in a sea of inconsistency, the phrase so aptly used by Willett (14) to describe current knowledge about diet-cancer relationships, then prospective studies must be mounted in suitable populations. Given that in many societies, individual variation in diet tends to be relatively slight, the most appropriate population is one in transition from one standard of living or from one country to another (15). Such populations exist in, for example, Athens where a sizable portion of the population has migrated from rural areas (16) or in Australia where there are large migrant populations originating in Italy, Yugoslavia, Greece, and the British Isles (17). In the British Isles, the recent migrants are from the Indian subcontinent and the Caribbean; in the United States, they are from Asia and Latin America. In Israel, migrants have come from America, Africa, Asia, and Europe (18). Such populations frequently retain part of their traditional diet while gradually acquiring the habits of the host country. There is thus a window of time during which meaningful prospective studies can be undertaken; a window which, for Japanese and Chinese migrants to the United States, has been exploited more for cardiovascular disease than for cancer.

Such an investigation is a major, long-term investment implying the recruitment of at least 50,000 persons age, say, 45 to 55 years, who are required to be followed for the next 25 years. Ideally, the cohort members should be contacted every 3 to 4 years and dietary and other information updated. To contemplate such a study in an area without good cancer registration would be ridiculous (see below). If it is possible to take blood and urine samples from cohort members at periodic intervals, this can be stored and questions of molecular, biological, and biochemical pertinence may be answered on a case-control basis as they arise. Despite the logistic and other difficulties in undertaking such studies, the yield in terms of pertinent information must more than outweigh the cost. Such cohorts can be used for many studies, their value increasing as time advances. For example, the Framingham cohort (19) and the cohort of Harvard graduates are still yielding useful information. It seems remarkable that, while the long-term study is accepted as appropriate in other branches of biological science, such as forestry, there should be such reluctance to do so for humans. As Susser (20) points out, a perspective that always begins with disease may discover an array of causes but obscures the array of possible outcomes. For public health, a perspective that begins with environmental factors (say, contaminated water or social situation) and searches out the consequences leads to discoveries less likely to be made from the opposite perspective, another argument in favor of the prospective study. Yet, the epidemiologist proposing such studies has hitherto attracted little support.

Epidemiology and Basic Science

The chronic disease epidemiologist is increasingly recognizing the potential contribution of the biochemist and molecular biologist to his work, just as the study of infectious disease

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mandated collaboration with the microbiologist and virologist. The epidemiologist studying the effects of aflatoxin exposure in populations with a sizable proportion of hepatitis B carriers cannot obtain useful direct information by questionnaire on either aflatoxin exposure or the existence of the carrier state. Urinary aflatoxins represent the intake of the past 48 h. Albumin-bound aflatoxin gives a much better indication of the aflatoxin load over the past 60–90 days (21). There is currently no method which would give an estimate of the total aflatoxin exposure over the past few years: this would be welcome.

While subcutaneous fat biopsy can yield, via gas chromatography, the spectrum of fatty acids in the diet over the previous months, the total quantity consumed cannot be estimated. Nonetheless, by making known his needs to the basic scientist, the epidemiologist may foster research work in the areas of his interest. This is well exemplified by dietary fiber; epidemiological interest resulted in laboratory collaborators realizing the inadequacies of traditional concepts of the composition of feces and the nature of fiber, leading to new analytical techniques and separation of fiber into a series of non-starch polysaccharides. The gaps in knowledge about the chemical changes taking place as food moves along the intestine are being slowly filled by use of such innovative techniques as magnetic trapping microcapsules (22). Such capsules have shown that modest alterations in the composition of human diets fed to mice can influence the level of colonic nuclear aberrations induced by benzopyrene.

The increasing availability of short-term *in vitro* tests for carcinogens in general, and nongenotoxic carcinogens in particular, using for example BALB/c 3T3 cells (23) may direct the attention of the epidemiologist to hitherto unexamined risks.

As mentioned several times in this paper, the mechanisms underlying the causation of breast cancer remain essentially unknown. While the most rational interpretation of descriptive and other evidence is that diet- and reproduction-associated events are important and that these probably exercise their effect through endogenous steroid hormones, much of the biochemical evidence has been difficult to interpret. The finding by Apter *et al.* (24) that some of the endocrine characteristics of early menarche, a risk factor for breast cancer, are preserved into adulthood suggests a causal role for serum estradiol and sex hormone-binding globulin. This type of study again exemplifies the need to follow cohorts over a long period of time. Given current social pressures (*e.g.*, in China), it is unlikely that the average age of first full term pregnancy, a major risk factor, will fall.

While endogenous steroid hormones have long been linked with breast and endometrial cancer risk, the concept that carcinogens could be formed endogenously from apparently innocuous dietary constituents such as nitrate and secondary amines is rather new. The significance of the endogenous formation of nitroso compounds is being studied in groups of contrasting gastric cancer risk in Japan and elsewhere following the development of a sensitive procedure to quantitate human exposure (25). This assay is based on the excretion of *N*-nitrosoproline as an index of endogenous nitrosation following ingestion of dietary precursors.

Transplacental exposures have been largely neglected by the epidemiologist, inquiries being confined to the offspring of smoking mothers and the effect of parental exposure to hydrocarbons, diethylstilbestrol, and ionizing radiation (26). Yet, in the experimental animal, fetal c-Ha-*ras* oncogenes can be transplacentally activated through a specific point mutation, postnatal promotion, however, being essential for the production of skin tumors (27). It is possible that this is a widespread phenomenon but the lack of substantial international variation in childhood cancer (28) has been held to reflect the importance of genetic rather than environmental influences. From the human point of view, regular monitoring of pregnancies would be required. If attention is confined to childhood cancer, for a population with a cumulative incidence up to age 15 years of 1 in 600, a sample of 8500 children followed for 15 years would be needed to have a 90% chance of detecting a 2-fold increase in the population rate with a statistical significance level of 5%. If only leukemia, the commonest form of childhood cancer, were considered, the numbers would have to be tripled. Preservation of biological material such as cord blood lymphocytes for examination on a case-control basis is theoretically possible but the sheer logistic effort would be enormous. As many cancers would be likely to appear after the death of the mother, records and material would need to be kept for a very long time. The influence of maternal exposures could be enhanced or offset by those experienced by the offspring after birth.

The application of many of these assays to epidemiological work may be difficult. By the time a technique becomes appropriate for epidemiological studies, it may have lost its frontiers of research interest to the basic scientist who, further, may not be interested in examining large numbers of specimens using costly and difficult to obtain materials. Fortunately some techniques can be largely automated.

The animal model must not be ignored; the interaction of aflatoxin and hepatitis B can be studied in the wood chuck or Pekin duck by a rigorous experimental approach, impossible in humans. Findings may not be entirely applicable to humans, but this would emerge from epidemiological studies.

Genetic Epidemiology. Harper (29) believes that genetic epidemiology has the potential for expanding the horizons of fields such as nutrition and for contributing to the development of new directions in medical and public health policy.

The current investigation of relatively rare familial disorders such as MEN-II is allowing the development of the expertise, reagents, and methods that will eventually be focused on the more common cancers such as those of the breast. This may result in characterization of a risk profile which would warrant close monitoring of affected individuals. As the potential for identifying subpopulations with unique genetic characteristics expands, it would become possible to classify individuals on the basis of potential susceptibility rather than on the basis of risk factors which, although they may be predictive of incidence on a population basis, are of unknown predictive value when applied to an individual.

From the epidemiological point of view, possibly the most useful techniques will be those linking pharmacogenetic variation to cancer risk. Three of these polymorphisms show an apparent association with malignancy: (*a*) acetylation; (*b*) debrisoquine 4-hydroxylation; (*c*) the *Ah* locus.

The slow acetylator phenotype among chemical dye workers exhibited an increased risk of bladder cancer. More recent studies suggest that the rapid acetylator phenotype is more likely to develop colorectal cancer. Those metabolizing debrisoquine extensively have been reported to have a disproportionately higher risk of lung cancer among cigarette smokers, and individuals with high aryl hydrocarbon hydroxylase inducibility in lymphocytes have been suspected of exhibiting an increased risk of cigarette smoke-induced lung cancer. Rapid highly sensitive tests for measuring alkyltransferase repair activity in small samples may provide another tool for screening popula-

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tions (30) for susceptibility to cancer induced by alkylating agents.

As more such associations become known, one can ask the following questions: how large are the genetic compared to environmental contributions to individual cancer risk? How great is the genetic variability between individuals? Questions which for resolution require the integration of laboratory methods and epidemiological studies. From a prevention standpoint should such polymorphisms be examined routinely at birth, like phenylketonuria testing, and what information should be given to the individual concerned? Intuitively, one might imagine that those told that smoking would for them carry a higher risk of lung cancer than normal would refrain, but this is by no means certain. If the possession of a particular polymorphism involved an increased risk for a proportion of those affected, the road to needless occupational discrimination in recruitment would be open.

Oncogenes. Taylor (31) reviewing applications of oncogenes to epidemiological studies stated "research on human oncogenes has been restricted to modest-size laboratory studies, but assays have now reached a point at which large clinical and population-based studies are practical. These studies will require close collaborative efforts by clinicians, epidemiologists, and molecular biologists and will be critical to the development and integration of this area of molecular biology into the field of medicine." To date, about 50 oncogenes have been identified from a variety of animal and human tumors, consistently appearing, sometimes with high frequency, in many cancers, *e.g.*, Ki-*ras* in pancreas cancer. The protooncogene homologues, about 30 in number, are to be found on specific regions of human chromosomes, nearly every chromosome carrying at least one protooncogene. Human tumor cells are characterized by a set of mutations which correspond to the activation of oncogenes or the inactivation of tumor suppressor genes. Every major human tumor has been found to contain oncogenes which, although diverse in function, appear to exert control over cellular replication and differentiation. The ability to detect oncogenes in fixed pathological material opens the possibility of what might be designated paleooncogenology and comparisons between differing populations could be indicative of ethnic differences in cancer. The biochemical consequences of oncogene activation are being intensely studied.

Animal studies strongly suggest that chemical carcinogens can directly activate oncogenes with considerable specificity such that one chemical will produce a characteristic mutation in the activated oncogene, while another will produce a different activating mutation. These findings are held to be in line with the multistage model of carcinogenesis. The activation of the oncogene may be the initiating step but promotion, additional oncogene activation, or some other modification of the cell probably still need to take place before a tumor develops. The oncogenes have their antithetical counterpart in the tumor suppression gene well exemplified by the familial form of retinoblastoma.

Taylor (31) suggested that oncogenes may serve as indicators of etiology. Unlike DNA adducts, which are transient and reflect only recent exposure, oncogene mutations persist and may be detectable in the tumor tissue. However, controls would be a problem because oncogenes would not be activated in normal tissue and the control would have to be another person with the same type of tumor not exposed to the agent in question. One could imagine the use of oncogene assay when claiming compensation for cancer said to be due to specific industrial exposures (31).

Oncogenes are in a sense a form of biological marker and may represent "signals in a continuum of events between a causal exposure and the resultant disease" (32). The conceptual framework for the validation and use of such markers has recently been reviewed by Schulte (33).

The epidemiologist wishing to take advantage of molecular biological and genetic techniques may find the topic immensely complex involving use of an arcane notation and illustrated by cabalistic diagrams purporting to enhance understanding. The neophyte must try to obtain a general vision before plunging into the forest. The article by Currie (34) on cancer prevention and the new biology constitutes an excellent introduction.

Prevention

While a given risk factor is likely to operate nearly everywhere, the arguments and approaches to be used in different societies to motivate the changes in behavior and improve work conditions and the general environment are likely to vary from place to place, and research into the optimum methods for convincing public and governments to take action is all too scanty.

Cancer levels are not immutable. It is likely that the incidence of gastric cancer at the turn of the century in the United States was as high as it is in present-day Japan, which would imply a fall in incidence in males from about 100 per 100,000 each year to one-tenth of that figure, *i.e.*, by about 1% *per annum*. Breast cancer levels, rising at some 5% per year, in Japanese now living in Hawaii are currently over double those in Japan (around 20) where the rate of increase is now about 3%. For prostate cancer, the current differentials in risk are even greater than for breast cancer, with an age-standardized incidence of around 7 in Japan, close to 30 in Hawaii Japanese, about 50 in United States Whites and around 90 in United States Blacks. Given the age distribution of prostate cancer, the effects of increases in incidence would be likely to occur some 20 years later than for breast cancer. Hence the interest in birth cohort analysis and scrutiny of changes in risk in younger age groups (45–59 years, 50–54 years) to see whether trends are in an upward or downward direction. Nonetheless, overall increases of some 3–5%/year have been observed in the populations cited. Incidence in Great Britain, however, has been stable for many years.

As Muir *et al.* (35) and Doll (36) have stressed, younger age groups are those which should be monitored as it is here that the effects of the appearance of a new carcinogen or the disappearance of an old one are first seen. To quote Doll (36): "If we can monitor populations with many millions of people, small effects can be detected quite quickly in young people in whom the incidence of disease is necessarily determined only by exposure in the relatively recent past. If, however, we want to be sure that we are avoiding disease as well as treating it more effectively, we shall need to have good systems for monitoring incidence, as trends and mortality become increasingly determined by improvements in therapy."

Unfortunately, in many parts of the world, cancer registration is still very difficult in that concepts of so-called confidentiality place needless barriers in the way of effective registration and the absence of nominal access to death certificates deprives a registry of one of its most useful means for determining completeness of coverage.

Assessing the Effect of Dietary Intervention. The evidence from studies of migrants supported by time trends and analytical epidemiological investigations strongly suggests that some

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items or components of diet are associated with cancer of the stomach, breast, large bowel, and prostate.

Not only is diet notoriously difficult to estimate, particularly fat, but there is not yet a consensus on the optimum method of analyzing dietary studies; *e.g.*, should the influence of a dietary item be corrected for total calories? Assuming that the common cancers are shown to be diet determined, it is salutory to assess what the results of intervention might be. The consumption of food is not an "all or none" phenomenon, although various groups eschew dietary items such as meat. Wahrendorf (37) has studied the likely effects of shifting consumption of dietary items, currently believed from case-control studies to influence cancer risk, from one quintile to another. Results are in a sense rather disappointing in that while one normally expects abolition of the tobacco habit to eventually result in an 80% or greater fall in lung cancer, the reductions to be expected by manipulating current diets appear to be in the order of 15–50%. Given the current imprecision in dietary assessment, case-control studies to determine whether intervention measures have worked may not succeed, success may only be measurable, and that indirectly, through time-trend analysis. Alternative strategies would be randomized trials in selected populations or via the prospective studies mentioned above. For the former, there is always the possibility of "contamination," those assigned the "old" diet adopting the "new" on the grounds that it could be beneficial.

To date there has been one rigorously controlled dietary intervention, a study mounted in North China (38). The population, ages 35–64 years, of an area with a very high incidence of esophageal cancer agreed to be randomized between treatment by placebo and a mixture containing riboflavin, retinol, and zinc. Compliance was strictly supervised and blood samples taken at the end of the third month showed that biochemical changes expected had indeed taken place. At the end of 13 months, over 90% of both groups agreed to endoscopy and biopsy. When the code was broken, there appeared to be no difference in terms of precancerous change in the esophageal mucosa between treatment and control groups. However, improvements in biochemical status in individuals was correlated with improvement in histological markers such as hyperkeratosis and acanthosis. These groups will of course have to be followed for a much longer period of time.

Once the dietary basis for these common cancers is reasonably well established, the question arises of persuading the public to change their eating habits. This has been tried extensively in connection with coronary heart disease in Karelia in Finland (39) being reinforced by changes in the fat content of milk and sausage. The food industry tends to be conservative and unwilling to change unless there is pressure from public and government and the prospect of profit. Governments are notoriously difficult to move, yet dietary patterns do change (40) and can be changed. To cite but one example, the increasing availability of high-fiber foods for which there is perceived to be a need and a market.

The Cancer Vaccine. The discovery by case-control and prospective cohort studies that carriers of the hepatitis B virus had a risk of primary liver cancer some 50–200 times greater than noncarriers, and the development of suitable plasma-derived and recombinant vaccines offers hope that primary liver cancer, currently in 8th rank in global incidence in males and representing an estimated quarter million new cancers each year, can be effectively prevented, even though there will still remain those associated with aflatoxin exposure, alcohol, smoking, and perhaps some oral contraceptive pills.

The evaluation of the efficacy of these vaccines in the control of the carrier state can be achieved in some 5–10 years. It will be difficult to demonstrate a protective effect against primary liver cancer before 30 years have elapsed. Such a study is now under way in The Gambia in West Africa, coordinated by IARC, and funded by the Department for Cooperation and Development of the Ministry of Foreign Affairs of Italy (41, 42). While vaccination for hepatitis B bolsters the program of normal childhood vaccinations, and *vice versa*, there is a possibility that vaccinating children may render them more susceptible to infection by hepatitis B around the age of 10 to 12 years. While the carrier state is less likely to develop at this age, this possible complication will have to be watched closely and revaccination may be needed.

As mentioned above, cancer of the cervix uteri is by far the commonest cancer in women of the developing world, with some 370,000 new cases each year. The discovery by techniques of molecular biology that the HPV, types 16 and 18, is much commoner in these tumors than in controls, again gives rise to the hope that an effective vaccine may be found, although Munoz *et al.* (43) felt the epidemiological evidence for a causal association was still inadequate. Nonetheless, the lack of reproducibility between "good" laboratories, not only insofar as type is concerned but also as to whether a HPV is present, is disturbing (44), as is the finding that the prevalence of HPV 16/18 in cervical cells in random population samples of women in Denmark and Greenland (where cervical cancer risk is some 6 times higher) was substantially greater in the lower risk population (45).

The problems, however, of the evaluation of a vaccine against HPV will be considerable. If the vaccine is derived from killed virus, will it be sufficiently protective to prevent viral colonization of the cervical epithelium? If the vaccine is based on a live mutant variant (as for Marek's disease of chickens) or on vaccinia virus incorporating an appropriate portion of the HPV molecule, how can one ensure that these too will not induce neoplasia. While screening could be carried out in nonhuman primates, absolute safety would be difficult to ensure and an untoward complication might take many years to emerge.

The case-control technique could be used to assess the efficacy of the vaccine; if effective, there should be a lower proportion of nonvaccinated among cases than among controls, but this would take several years to evaluate. The time of delivery of the vaccine could be critical and, as for cervical cancer cytology screening programs, it is quite possible that it is the groups already at low risk that would seek vaccination. Alternatively, if the high risk groups selectively sought vaccination (as in breast cancer screening), the evaluation would be biased in the other direction. Under the first assumption, the vaccine would be falsely effective; in the second, the efficiency would be underestimated. For a prospective follow-up, Higginson *et al.* (46) examined the sample sizes that would be needed, taking into account vaccine efficiency.

It is quite possible that some forms of childhood leukemia will be shown to be virally induced, in addition to the human T-cell leukemia virus induced variant of the disease. Again, it may be possible to produce a vaccine, but the same questions of safety would arise and if the proportion of childhood leukemia caused by a virus was rather low, then evaluation would be very difficult even if the case-control approach were used, inasmuch as this would imply the ability to separate virally induced leukemias from the others.

That nasopharynx cancer is in some way linked to exposure to the Epstein-Barr virus in susceptible communities, such as

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Cantonese, is now well established. If it be assumed that, as for infectious mononucleosis, it is those who are infected late who are at greatest risk, perhaps 10% of the population, then it is possible that only the seronegatives would be protected by vaccination. Because it would be impracticable to test an entire population, vaccination would have to be for everyone whether seropositive or not. To evaluate the effectiveness of vaccination would be virtually impossible unless the vaccine was 100%, or close to 100%, efficient. Higginson *et al.* (46) present the statistical basis for these statements.

While more could be done to apply to preventive ends what is already known about causation, despite major epidemiological and laboratory effort over the last two decades, specific preventive measures cannot be recommended with any certainty for about 50% of cancers in males and possibly as much as 70% in females. Higginson (47) observed that, in the United States at least, there currently seem to be two control strategies: (*a*) regulatory programs designed to control or eliminate minute quantities of pollutants in the ambient environment, based on fairly rigid quantitative risk assessment (in which he has little faith); (*b*) a biological research effort to understand the fundamental biological mechanisms with the objectives of eventually manipulating or interfering in carcinogenesis through chemoprevention and therapy. He considered that the eliminatory approach would have little impact on the burden of cancer and that the mechanistic avenue, although difficult and slow, represented the most logical alternative. A major barrier to the second approach may lie in the similarity between normal cell metabolism and that of the not-quite-normal cell on the road to transformation. Will it be possible to find a chemical corrective which would be selective for the latter? Once an oncogene has slipped the leash and the malignant process has begun, can the damage be undone by reactivating the suppressor genes? Further along the malignant process, the only treatment(s) available today seems to be those leading to cell death. The various attempts to harness immune and other defense mechanisms may have had success in a few patients; they have not influenced mortality significantly.

Comment

In a journal which is still largely devoted to what might be denoted basic cancer research, it may seem egregious to draw attention to the fact that all of the known causes of human cancer have hitherto been discovered by epidemiologists. In the future their continued success will increasingly demand the support of their colleagues in clinical, basic, and applied research. Many of those controlling funding for research come from a clinical or basic research background and, not unnaturally, tend to support these disciplines. A conscious effort is needed to foster epidemiological research even though this implies a reduction in support for other areas.

Vandenbroucke (48) reminds us that epidemiologists who, in the tradition of John Snow, subscribe to the view that disease can be prevented without the need to have detailed knowledge of pathogenetic mechanisms are destined to be the losers in a struggle with a superior scientific idea. For the miasmists that competing idea was the germ theory of disease; for the epidemiologist of today, in his view, it is molecular biology.

Much of what is denoted basic cancer research today yields quick, fascinating, and frequently abundant answers which are held to be steps on the road to the solution of the cancer problem via an understanding of mechanisms. It is not always evident that much of this information leads, or will ever lead, to improvements in cancer prevention, diagnosis, or treatment, despite the enormous intellectual, conceptual, and financial investment which is entailed. Such an iconoclastic assertion could well be proved wrong over the next decade: the colony-stimulating factors of Metcalfe (49) and Sachs (50) may result in the reversal of established leukemia and exploitation of the phenomenon of intracellular communication (51) in improved results in chemotherapy. The control of oncogene repressors may become feasible, etc. Nonetheless, the imbalance in effort and resource allocation between epidemiology and basic science is currently much too great.

As Smith (52) so aptly states, "Generally, the further you get from the molecule, the poorer the research effort becomes. The reason is lack of funding, status and trained researchers."

These reasons have already been discussed in some detail (53) and form a closed circuit which is difficult to break. Gordis (54) identifies another cause for concern in the extent to which peer review criteria may become excessive and hard to control. Quoting Voltaire who said that "the best is the enemy of the good," he implies that review groups by insisting on perfection may stifle innovation, concluding that "the fostering of creativity and imagination in epidemiology is our most important challenge." Stolley (55) pointed to an inability or an unwillingness on the part of some epidemiologists to synthesize available data coming from all fields that bear on the problem in hand; instead, he noted they placed extraordinary importance on small defects in study designs. Gordis continues, "epidemiology is not biostatistics and *vice versa* and there is a danger of a schism resulting in a profession divided into two groups—the medically qualified, sound in biology and poor in statistics and the statistically qualified, weak in biology." This argues strongly for the existence of a critical mass of epidemiologists drawn from both backgrounds if an institute is to be successful.

Epidemiology, like any other science, goes through phases of self-doubt and autocriticism. To quote Susser (20), "Present day epidemiology . . . is primarily an epidemiology of technique, at risk of existing for its own sake regardless of subject matter. It is epidemiology pursued as a vocation by accomplished professionals who deploy refined and complex methods. In the absence of a central concern with subject matter, the satisfactions of technical command are held within narrow bounds; in the absence of broader purpose, an arsenal of methods might not necessarily be directed to the benefit of the public health." Perusal of the successive volumes of the Annual Directory of Ongoing Research in Cancer Epidemiology (56) is depressing in that many studies are of the "i" dotting and "t" stroking variety.

The analysis of epidemiological studies continues to be increasingly dependent on the computer to "clean," marshal, and manipulate increasingly large and complex data sets. The interpretation of results remains based on a mixture of statistical indices and judgment (57). For the former, the *P* value is under increasing attack and the confidence interval of the relative risk which focuses on the effect size is no longer held to be adequate. The likelihood function, held to have a sound theoretical foundation as a basis for inference, has been suggested as appropriate [for discussion see the paper of Goodman and Royall (58)] and able to "move us permanently away from the notion that in the data is absolute proofs and truths that statistical technologies can reveal. Unlike the "*P*" value, the use of evidential measures forces us to bring scientific judgement to data analysis, and shows us the difference between what the data is telling us and what we are telling ourselves."

The problem of negative results remains with us. To quote

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Gordis (54) "investigators need to receive clear messages from the reward system—including funding sources, academic promotions committees, or any other sources of recognition—that publication of negative results is desirable and will be viewed as favourably as studies that generate positive results *provided the study is well conceived and designed and has been carried out in a rigorous fashion.*" A bias towards the publication of the positive result is more harmful than is realized. It is truly important to know that an exposure is likely to have little effect because this may have considerable influence on investment priorities. Even a large negative study could still be consistent with a 20% increase in risk (59) and a weakly positive study could also be consistent with the absence of an effect. Inadequate "positive" studies are continuously quoted. Begg and Berlin (11) cite the example of flurouracil as an adjuvant treatment for colorectal cancer. Although an early study using historical controls published as a leading article in a prestigious journal, demonstrating significant survival advantage, was not confirmed by several subsequent randomized trials, the drug still represents the conventional standard of care. In other words, a highly visible publication can have a dramatic and prolonged impact on medical practice even if the results are subsequently demonstrated to be unreliable. Gordis notes that several of these unresolved issues touch on the relationship of epidemiology to public policy, yet epidemiology is frequently still out in the cold. Even in an organization such as WHO, it seems necessary to remind member nations that epidemiology is in the wings waiting to come into the limelight and to be used (60).

Soskolne (61) has urged very convincingly for the creation of a written code of ethics for epidemiologists, observing that as the science of epidemiology impacts directly on the setting of standards for the regulation of population exposures to possibly hazardous substances, and hence on interpretations and rulings in matters of law, epidemiologists have a public responsibility perhaps even more significant than that of other scientists. Even though physician epidemiologists adhere to a medical code of ethics, these relate to patient care and are not directly relevant to population-based research. The International Statistical Institute (62) has adopted a "Declaration on Professional Ethics" which comprises four major rubrics: (*a*) obligations to society; (*b*) obligations to funders and employers; (*c*) obligations to colleagues; and (*d*) obligations to human subjects. These areas are clearly directly relevant to epidemiology. Many of these problems are discussed by WHO (63) in the context of environmental epidemiology. Because epidemiology is expected to provide the bulk of the answers that the scientist, workman, employer, citizen, and government need to know about the relationship between various aspects of environment and human health, it is of paramount importance that evaluation of risk be as impartial as possible. The example of the Monographs program of the IARC is worth following; assessment by an international group of experts is less likely to be biased than the opinion of a single individual. Although the IARC addresses only qualitative risk, the same approach could be extended to quantification.

Although the world is full of migrant populations, little has yet been done to exploit their differences in cancer risk from those of the countries of origin and settlement. False issues of confidentiality continue to block epidemiological research in many countries, notably those of western Europe where access to the death certificate by name continues to be prohibited, thus effectively strangling the cohort study. Many of those who campaign actively for yet further restrictions on confidentiality are the same as those who demand, and rightly so, that the environment be as carcinogen free as possible. They do not see, or do not wish to see, the contradiction of their standpoints.

The increasing likelihood that to reduce the "greenhouse effect" more and more electrical power will be generated from nuclear sources demands that the effects of low dose radiation be measured, an assessment which paradoxically is possibly best made within the nuclear power industry. However, the effects of low level exposure to ionizing radiation are never likely to be resolved and decisions will have to be taken on other grounds. Better methods are needed to detect clusters. The significance of the temporal increase in asbestos bodies found in lungs of many populations remains obscure. Despite the damage done by atmospheric pollution to buildings and nature, this would appear to be carcinogenic only in smokers. Are low doses of carcinogen from several sources additive or multiplicative or indeed are some antagonistic? The true level of risk associated with passive smoking is still not known. The recent report that those smoking involuntarily have an increased risk of cancer of the cervix uteri requires confirmation, although the increase in risk in smokers is now well established (64).

In proposing preventive measures, many still fall into the relative risk trap, failing to recognize that a widespread exposure associated with a small relative risk, affecting a total population, may result in more cancers than a very high risk in a small segment of the population. Thus, cleaners of vinyl chloride polymerization kettles had a relative risk of hepatic angiosarcoma of some 400-fold. Yet the total number of such tumors in the world literature is less than 100; a relative risk of 1.5 affecting one-half of a population could result in many thousands of tumors. Obviously occupational risks must be prevented as soon as identified but they should not be used to divert attention from other issues like tobacco.

The priorities for the next 10 years are what Muir (53) stated them to be in 1983: to determine how diet and other elements of life-style influence risk for the very common cancers of the digestive and genital tracts. While the "cancer wheel" to be found on the walls of many research units in the 1970s has fallen out of fashion, nonetheless, small portions of the puzzle have been filled in. As in the past, progress will be made by the development of a series of blind alleys which, once identified, lead to the now obviously correct approach, a kind of variant of catastrophe theory. In science, the road to the truth is paved with other men's misapprehensions.

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